Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 10

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the tenth volume in that series. AEGL documents for *N,N*-dimethylformamide, jet propellant fuels 5

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

and 8, methyl ethyl ketone, perchloromethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the NAC authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The six interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the six committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for *N*,*N*-dimethylformamide (fourteenth interim report, 2006), jet propellant fuels 5 and 8 (seventeenth interim report, 2010), methyl ethyl ketone (twelfth and fifteenth interim reports, 2005 and 2008, respectively), perchloromethyl mercaptan (fifteenth interim report, 2008), phosphorus oxychloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), phosphorus trichloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), and sulfuryl chloride (sixteenth interim report, 2009): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr. (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Kenneth Still (Occupational Toxicology Associates, Inc.), and Bernard M. Wagner (New York University Medical Center [retired]).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the eleventh interim report was overseen by Rakesh Dixit

(MedImmune/AstraZeneca Biologics), and the twelfth interim report was overseen by David Gaylor (Gaylor and Associates, LLC). The review of the fourteenth, fifteenth, sixteenth, and seventeenth interim reports was overseen by Robert Goyer, University of Western Ontario (retired). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke and Iris A. Camacho (both from EPA) and George Rusch (Honeywell, Inc.). The committee also acknowledges Keegan Sawyer, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Orin Luke (senior program assistant), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

Dedication

The subcommittee dedicates this series of reports to our late colleague
and co-founder of the Acute Exposure Guideline Levels program,
Dr. Paul Tobin,
whose 31 years of distinguished service with the
U.S. Environmental Protection Agency in the fields of chemistry,
toxicology and health-risk assessment contributed significantly to scientific
knowledge, to the development of the Acute Exposure Guideline Levels
program, and to the protection of public health and safety.

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National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the tenth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data

for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the

AEGL reports. Thus far, the committee has prepared nine reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b). This report is the tenth volume in that series. AEGL documents for *N*,*N*-dimethylformamide, jet propellant fuels 5 and 8, methyl ethyl ketone, perchlormethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

5

Phosphorus Oxychloride[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter] mg/m^3]) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-

[1]This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory) and Tom Hornshaw (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGLs represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Phosphorus oxychloride is a colorless fuming liquid with a pungent odor. It is stable to over 300°C but is highly reactive with water yielding phosphoric acid and hydrogen chloride. It is used in the manufacture of plasticizers, hydraulic fluids, gasoline additives, fire-retarding agents, and in the manufacture of alkyl and aryl orthophosphate trimesters.

Information regarding exposure of humans to phosphorus oxychloride are qualitative reports that indicate notable dermal, ocular, pharyngeal, and pulmonary irritation following acute and subchronic (intermittent) exposures. Most reports lacked exposure concentrations, with the exception of one report of occupational exposure to phosphorus oxychloride of 1.6-11.2 ppm. Effects often persisted after cessation of exposure, especially in individuals experiencing more severe effects. Neither odor detection data nor lethality data are available for humans.

Quantitative data in animals are limited to reports of lethality. These data include a 4-h LC_{50} (concentration lethal to 50% of test animals) of 44.4 ppm for rats and 52.5 ppm for guinea pigs, and an unverified 4-h LC_{50} of 32 ppm for rats. A 5-15 min exposure of rats and guinea pigs to phosphorus oxychloride at 0.96 ppm was stated to be a “threshold response” in one report. A brief report from industry indicated immediate adverse responses (at 2 min) and death (18 min) after exposure to a very high concentration (25,462 ppm). The studies affirm the extreme irritation properties of phosphorus oxychloride, although the exposures

described also resulted in lethality. No information was available on reproductive and developmental toxicity, genotoxicity, or carcinogenicity.

There are no definitive data regarding the metabolism or precise mechanism of action of phosphorus oxychloride toxicity. On the basis of the available human and animal toxicity data and the chemical properties of phosphorus oxychloride, it was assumed that the primary effect is damage to mucosal surfaces and, for respiratory effects, subsequent pulmonary edema. The lethal potency of phosphorus oxychloride, however, does not appear to be explained simply by the action of its degradation products (phosphoric acid and hydrogen chloride).

AEGL-1 values were not derived for phosphorus oxychloride. No human or animal data relevant to the derivation of any AEGL-1 for phosphorus oxychloride were located.

AEGL-2 values were not derived for phosphorus oxychloride. No exposure-response data relevant to the derivation of any AEGL-2 were located. Estimating AEGL-2 values by a reduction in AEGL-3 values was considered tenuous and difficult to justify in the absence of such data.

AEGL-3 values were developed using an estimate of the lethality threshold on the basis of a 4-h LC_{50} of 48.4 ppm in rats (Weeks et al. 1964). Although exposure-response data were unavailable, the lethality threshold was estimated as one-third of the 4-h LC_{50} (48.4 ppm ÷ 3 = 16.1 ppm). This is also justified because many respiratory tract irritants have exposure-response relationships in which the transition from progressive irritation and repairable epithelial tissue damage to lethal pulmonary damage occurs abruptly. Because of uncertainties regarding species variability in the lethal response to phosphorus oxychloride and the lack of lethality data in humans, an order-of-magnitude uncertainty adjustment was applied for interspecies variability. Contact irritation resulting in damage to mucosal surfaces appears to be involved in the toxic response to phosphorus oxychloride. This response is probably a function of the extreme reactivity of phosphorus oxychloride and its dissociation products with tissues (especially pulmonary mucosal surfaces), and probably does not vary greatly among individuals. Therefore, the uncertainty adjustment selected for intraspecies variability was 3. A larger uncertainty factor would result in AEGL-3 values that are inconsistent with human data. The concentration exposure and time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of an empirically-derived exponent (n), conservative and protective AEGL values were calculated by temporal scaling; n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

The AEGL values for phosphorus oxychloride are presented in Table 5-1. The range of interspecies variability remains uncertain because of sparse animal data and the lack of quantitative exposure-response data for humans. The lack of exposure-response data for nonlethal effects in animals or humans is a significant data deficiency.

1. INTRODUCTION

Phosphorus oxychloride is a colorless, clear, fuming liquid with a musty, pungent odor. No odor threshold data are available. Phosphorus oxychloride is a chlorinating agent used in the manufacture of plasticizers, hydraulic fluids, gasoline additives, and fire retarding agents (O'Neil et al. 2001). It is also used extensively in the manufacture of alkyl and aryl orthophosphate triesters. The physicochemical data on phosphorus oxychloride are presented in Table 5-2. The chemical is stable to >300ºC but is highly reactive with water yielding phosphoric acid and hydrogen chloride. The decomposition reaction is:

$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl$$

TABLE 5-1 Summary of AEGL Values for Phosphorus Oxychloride[a]

Classification	10 min	30 min	1 h	4 h	8h	End Point (Reference)
AEGL-1 (Nondisabling)	Not recommended					
AEGL-2 (Disabling)	Not recommended					
AEGL-3 (Lethality	1.1 ppm (6.9 mg/m^3)	1.1 ppm (6.9 mg/m^3)	0.85 ppm (5.3 mg/m^3)	0.54 ppm (3.4 mg/m^3)	0.27 ppm (1.7 mg/m^3)	Estimate of lethality threshold in rats (16.1 ppm); 3-fold reduction in 4-h LC_{50} of 48.4 ppm (Weeks et al. 1964)

[a]Absence of AEGL-1 and AEGL-2 values does not imply that exposure below the AEGL-3 is without adverse effect.

TABLE 5-2 Chemical and Physical Data for Phosphorus Oxychloride

Parameter	Value	Reference
Synonyms	Phosphoryl chloride, phosphorus chloride, phosphorus oxytrichloride, trichlorophosphine oxide, trichlorophosphorus oxide	Fee et al. 1996; O'Neil et al. 2001; RTECS 2009
CAS registry number	10025-87-3	O'Neil et al. 2001
Chemical formula	$POCl_3$	O'Neil et al. 2001
Molecular weight	153.33	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Melting point	1.25°C	O'Neil et al. 2001
Boiling point	105.8°C	O'Neil et al. 2001
Density	1.645 at 25°C	O'Neil et al. 2001
Solubility	Decomposes in water and alcohol	Fee et al. 1996
Vapor pressure	40 mmHg (27.3°C)	HSDB 2009
Conversion factors in air	1 ppm = 6.27 mg/m^3 1 mg/m^3 = 0.16 ppm	NIOSH 2005

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding the acute lethality of phosphorus oxychloride in humans.

2.2. Nonlethal Toxicity

Most information on acute exposure of humans to phosphorus oxychloride is from secondary sources (ACGIH 1991; O'Neil et al. 2001). The following signs and symptoms were reported for acute exposures: headache, respiratory tract and eye irritation, chest pain, dyspnea, and nephritis. Chronic asthma-like conditions after acute exposure have also been reported (Sassi 1954; HSDB 2009). However, exposure-response data for these responses are lacking. Although there are no reports that provide quantitative data appropriate for AEGL development, they do affirm that the respiratory tract is a primary target for toxic responses following acute inhalation exposure to phosphorus oxychloride.

An accident involving an explosive release of phosphorus oxychloride, hydrogen chloride, oxalic acid, phosphorus pentachloride, and oxalyl chloride was reported by Rosenthal et al. (1978). Eight men and three women, ages 22-56 years, were exposed for approximately 30 sec to 2 min (the time required to escape from the contaminated area). The major signs and symptoms of exposure were wheezing, shortness of breath, conjunctivitis, and coughing. Nine people exhibited effects on ventilatory function; six recovered within a few days. In the other three individuals, disturbances in respiratory function returned to normal after 4 wk in one patient and 2.5 mo in the second, but persisted after 2 y in the third patient. The applicability of this report to AEGL development is questionable because of the lack of data on exposure concentrations and of concurrent exposure to other chemicals that have similar toxic effects.

Sassi (1954) described 20 cases of acute and subchronic occupational exposure in the manufacture of phosphorus oxychloride. Exposure concentrations varied from 10-20 mg/m^3 (1.6-3.2 ppm) for normal conditions to 70 mg/m^3 (11.2 ppm) for accidents. The signs and symptoms of acute exposures included irritation of the eyes and throat, dyspnea, dry cough, and bronchial stenosis (occurring several days after exposure). Long-term exposures resulted in more severe effects, including conditions characterized as asthmatic bronchitis and emphysema. Although concentrations for various exposure situations were provided in the report, there were no information on exposure durations.

Velsicol Chemical Corporation (1978) reported eye irritation in a worker exposed to phosphorus oxychloride. No information was provided on the concentrations to which the worker was exposed nor the severity of the irritation. The worker did, however, return to work; a 3-d "probable length of disability" was noted.

A health hazard evaluation conducted by the National Institute of Occupational Safety and Health (NIOSH) of the FMC Corporation plant in Nitro, West Virginia, reported that workers with known repeated exposures to phosphorus oxychloride or phosphorus trichloride experienced a significantly higher ($p < 0.001$) prevalence (65%) of respiratory symptoms (chest tightness, wheezing, difficulty breathing) compared with unexposed workers (5%) (Tharr and Singal 1980). However, no correlation was found between results of pulmonary function tests on the workers and exposure to these chemicals. The study involved 37 exposed workers and 22 unexposed workers. Most air samples were below detection limits, although one employee (wearing a chlorine gas mask) was exposed to phosphorus oxychloride at approximately 4 mg/m^3 for about 25 min; no effects reported for this individual.

A follow-up study by NIOSH on 26 of the exposed workers and 11 of the unexposed workers at FMC Corporation reported that half of the exposed workers reported significantly ($p < 0.002$) more episodes of respiratory effects (wheezing, breathlessness, and chest tightness) compared to the unexposed workers who reported no such effects (Moody 1981). Results of pulmonary function tests did not reveal significant effects from exposure to phosphorus oxychloride (or phosphorus trichloride). No significant difference in pulmonary function (FEV_1) was found in the exposed workers compared with the unexposed workers over a 2-y period. The small sample size reduces the power of the study to detect such changes and, therefore, compromises the apparent negative finding. Additionally, it appeared that the pulmonary function tests were performed after the occurrence of the symptoms noted in the questionnaires completed by the workers.

On January 22, 1984, approximately 6,500 gallons of phosphorus oxychloride were released from a large storage tank at a chemical plant in Sauget, Illinois, as a result of an icicle shearing a pipe nipple off the tank (T. Hornshaw, Office of Chemical Safety, Illinois EPA, pers. communication, 2009). The plume affected seven employees, and moved into neighboring Rush City, Illinois. Thirty five citizens were treated at area hospitals, most from a neighborhood approximately one-half mile from the plant. The most common signs and symptoms were respiratory tract irritation and stomach pain. Five citizens were admitted overnight but none were in serious condition, and were later released. All of the affected employees were examined by a company physician and were cleared to resume work the same day. No measurements of airborne concentrations were taken.

2.3. Developmental and Reproductive Toxicity

No human developmental and reproductive toxicity data concerning phosphorus oxychloride were found.

2.4. Genotoxicity

No human genotoxicity data on phosphorus oxychloride were found.

2.5. Carcinogenicity

No human data were found regarding the carcinogenic potential of phosphorus oxychloride.

2.7. Summary

Most information on the toxic response of humans to phosphorus oxychloride is from secondary reports that lack quantitative exposure-response data. The chemical appears to be extremely irritating to the respiratory tract and other mucous membranes. Both port-of-entry and systemic effects have been reported. Primary reports describe occupational exposures to phosphorus oxychloride, but they involve simultaneous exposures to other irritating chemicals (e.g., hydrogen chloride, oxalic acid, phosphorus pentachloride, oxalyl chloride) and lack information on exposure concentrations and durations. The reports affirm signs and symptoms of nasopharyngeal, ocular, and dermal irritation, and ventilatory dysfunction following acute exposures. Concurrent exposures to other chemicals, especially those having the same effects and targets as phosphorus oxychloride, compromise the usefulness of human exposure data for quantitative determination of AEGL values.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Quantitative data on the acute lethality of phosphorus oxychloride are from a single study in rats and guinea pigs, and an unverified 4-h LC_{50} value for rats.

3.1.1. Rats

Weeks et al. (1964) reported on the acute lethality of phosphorus oxychloride in female rats. The experimental protocol consisted of a group of 20 young adult female rats (strain not specified) exposed to phosphorus oxychloride (concentrations not provided) followed by a 14-d observation period. Another group of 20 rats was similarly exposed to phosphorus oxychloride and ammonia (for neutralization of hydrolysis products). The test vapors were generated by passing dried nitrogen through the liquid test article. The vapors were then mixed

with influent air before being pumped into the chamber. Test article concentrations were determined by collection and weighing of material on a filter. These samples were also analyzed for phosphorus, nitrogen, and chloride. The test atmospheres were calculated as microgram of phosphorus per liter of air (µg/L) and as micromoles of phosphorus oxychloride per mole of air (µmole/mole). The latter expression assumed no hydrolysis of the test material (hydrolysis, however, was calculated to be about 15%). During exposure, rats exhibited signs of irritation (pawing and scratching of the nose and head) and had porphyrin secretions around the eyes. Gasping and convulsions preceded death which occurred within 48 h. No further details were provided regarding time of deaths. The 4-h LC_{50} for rats was reported as 48.4 µmole/mole (48.4 ppm). Neutralization with ammonia lowered the 4-h LC_{50} to 44.4 µmole/mole (44.4 ppm). Although simultaneous exposure to ammonia reduced or eliminated signs of irritation, it resulted in gross and microscopic pathologic findings (dark red lungs, desquamation of respiratory tract epithelium, and plugging of bronchial and bronchiolar lumens). The LC_{50} values do not necessarily imply that the test material was in a vapor from. In fact, it is probable that vapor and aerosol forms were present in the exposure atmosphere. With the exception of the median lethal concentration values, no other exposure-response data were provided.

In a study by Molodkina (1974), acute inhalation exposure of rats to lethal or near-lethal concentrations of phosphorus oxychloride resulted in immediate signs of irritation (rubbing of faces and restlessness). The rats exhibited inactivity and decreased respiration after 5-15 min, followed by convulsions. Rats that survived showed continued lacrimation and corneal opacities, and ulcers around the mouth several days after exposure ended. The report identified a "threshold concentration" of 0.006 mg/L (0.96 ppm) on the basis of "integrated characteristics." It is unclear as to what effect this threshold pertains or the precise nature of the "integrated characteristics." Information in this report affirms the irritation and lethal capacity of phosphorus oxychloride after acute inhalation exposure.

Details regarding a 4-h LC_{50} of 32 ppm for rats in a 1972 study (Marhold 1972 as cited in RTECS 2009) were unavailable for analysis and could not be verified.

The results of an inhalation study in rats were provided in a brief report by Monsanto (1991). Male Sprague-Dawley rats (number not specified) were exposed to phosphorus oxychloride at 159.7 mg/L (25,462 ppm) for 18 min. Conditions in the 35-L chamber were: 25°C, 85% humidity, and 4.0 L/min airflow. The concentration of the test material was such that there was a fog in the chamber. Within 2 min the rats were having difficulty breathing and their eyes were closed. After 10 min, weakness, convulsions, and collapse were observed, and one rat died. All rats were dead after 18 min. Necropsy revealed lung congestion. No further details were provided.

3.1.2. Guinea pigs

Weeks et al. (1964) conducted experiments using groups of 10 male guinea pigs. The experimental protocol was the same as that described for the experiments with rats. The response of the guinea pigs was consistent with exposure to an irritating chemical (restlessness, lacrimation, pawing at nose and head). The 4-h LC_{50} was 52.5 μmole/mole (52.5 ppm). Deaths occurred within 48 h after exposure; no further details were provided. Neutralization of the phosphorus oxychloride with ammonia resulted in a lowering of the LC_{50} to 41.3 μ mole/mole (41.3 ppm). As in the study with rats, simultaneous exposure of the guinea pigs to ammonia appeared to decrease the irritation responses to the phosphorus oxychloride but increase overall toxicity. The series of exposures and the respective responses used to obtain the median lethal concentration were not provided and, therefore, no other exposure-response data are available.

The previously discussed (Section 3.1.1) study by Molodkina (1974) also examined the response of guinea pigs to acute inhalation of phosphorus oxychloride. Lacrimation and corneal opacities were reported for animals after acute exposure to lethal or near lethal concentrations. No other details were reported.

3.2. Nonlethal Toxicity

Definitive exposure-response data for nonlethal toxicity in animals were not available. Weeks et al. (1964) and Molodkina (1974) reported that acute inhalation of phosphorus oxychloride (for up to 4 h) by rats and guinea pigs resulted in severe irritation (rubbing of face, lacrimation, porphyrin secretions, desquamation of pulmonary epithelium), but the precise concentrations and exposure durations were not provided. The only exposure-duration data provided were median lethality values. Thus, it is difficult to determine concentrations of phosphorus oxychloride that might cause nonlethal responses without potential for lethality.

3.3. Developmental and Reproductive Toxicity

No animal developmental and reproductive toxicity data concerning phosphorus oxychloride were found.

3.4. Genotoxicity

No animal genotoxicity data on phosphorus oxychloride were found.

3.5. Carcinogenicity

No animal data were found regarding the carcinogenic potential of phosphorus oxychloride.

3.6. Summary

Quantitative exposure-response toxicity data in animals were from lethality studies rats and guinea pigs (Table 5-3). A report by Weeks et al. (1964) provided an adequate description of the experimental protocol and 4-h LC_{50} value for rats (44.4 ppm) and guinea pigs (52.5 ppm). A study by Molodkina (1974) also examined the toxic response of rats and guinea pigs to inhaled phosphorus oxychloride; exposure to phosphorus oxychloride at 0.96 ppm for 5-15 min was considered a threshold response. However, the characteristics of the responses or what constituted the "threshold" were not provided. A brief report from Monsanto (1991) showed immediate adverse responses (after 2 min) and death (after 18 min) after exposure to phosphorus oxychloride of 25,462 ppm. Acute lethality values from a secondary source could not be verified. The available studies affirm the extreme irritation properties of phosphorus oxychloride, although the exposure concentrations described also resulted in lethality. No information was available regarding reproductive and developmental toxicity, genotoxicity, or carcinogenicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the metabolism and disposition of phosphorus oxychloride were found.

TABLE 5-3 Acute Lethality of Phosphorus Oxychloride in Laboratory Animals

Species	Lethality Value	Reference
Rat	4-h LC_{50} = 48.4 ppm	Weeks et al. 1964
Rat	4-h LC_{50} = 32 ppm (not verified)	Marhold 1972 as cited in RTECS 2009
Rat	100% lethality = 25,462 ppm after 18 min	Monsanto 1991
Guinea pig	4-h LC_{50} = 52.5 ppm	Weeks et al. 1964

4.2. Mechanism of Toxicity

The precise mechanism of toxicity of inhaled phosphorus oxychloride has not been elucidated. The irritant properties of phosphorus oxychloride might be from its decomposition products, phosphoric acid and hydrogen chloride. However, the acute lethality of phosphorus oxychloride appears to be greater than from the decomposition products alone. For example, the 1-h LC_{50} values for phosphoric acid and hydrochloric acid in rats are >212 ppm and 3,124 ppm, respectively, whereas the 1-h LC_{50} for phosphorus oxychloride is 76 ppm (estimated by temporal extrapolation from 4-h data). Although the acute lethality of inhaled phosphorus oxychloride probably results from damage to the respiratory epithelium and pulmonary edema, the role of delivery to this target tissue remains uncertain. Exposure to phosphorus oxychloride might allow the formation of larger concentrations of phosphoric acid and hydrochloric acid in the lungs than would be possible from exposures to each of the chemicals alone. This would cause greater damage and explain, in part, the greater toxicity of phosphorus oxychloride.

4.3. Structure-Activity Relationships

Barbee et al. (1995) conducted an acute toxicity study in which groups of 10 rats were exposed to oxalyl chloride $(COCl)_2$ at 0, 462, 866, 1,232, 1,694, or 2,233 ppm for 1 hr. The 1-h LC_{50} was 1,840 ppm. The acute lethality of oxalyl chloride was similar to that of hydrogen chloride, but oxalyl chloride was much less toxic than phosphorus oxychloride. Because the toxicity of phosphorus oxychloride appears to be greater than that of hydrogen chloride, it is unlikely that the mechanisms of toxicity for the two chemicals are the same. Thus, the development of AEGL values on the basis of analogy to hydrogen chloride production alone might underestimate the toxic potential of phosphorus oxychloride.

Phosphorus trichloride produces many of the same signs and symptoms as phosphorus oxychloride after acute inhalation exposures (Weeks et al. 1964; ACGIH 1991) and also undergoes rapid hydrolysis to hydrogen chloride and phosphonic acid. Data from rats and guinea pigs (Weeks et al. 1964) suggest that the lethal potency of phosphorus oxychloride might be similar to that of phosphorus trichloride. The rat 4-h LC_{50} values for both chemicals are approximately 50 ppm which supports the contention that they have similar toxicity. Information on human exposures to phosphorus trichloride verify a potential for irritation of the respiratory tract, nasopharyngeal region, eyes, and skin, and effects on ventilatory function (Wason et al. 1982, 1984). These human exposure reports provide qualitative information on the toxic response to the chemical, but lack measurements of exposure.

4.4. Other Relevant Information

4.4.1. Species Variability

Data are insufficient to reliably describe species variations in toxic responses to inhaled phosphorus oxychloride. Rats and guinea pigs appeared to respond similarly in a study by Weeks et al. (1964) and on the basis of an unverified LC_{50} in rats (RTECS 2009).

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues of special concern have been identified that would directly affect the derivation of AEGL values for phosphorus oxychloride. Simultaneous exposure to other irritating or corrosive chemicals would necessitate adjustments in emergency response planning for potential exposures to phosphorus oxychloride.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative exposure-response data in humans are not available for development of AEGL-1 values for phosphorus oxychloride. Information on the human experience is based on qualitative descriptions of signs and symptoms of acute exposure. Although exposure concentrations were not provided, the available reports indicate that very short exposures might result in notable respiratory, ocular, and dermal irritation. There is evidence that respiratory effects might persist for an extended period after exposure is ceased.

5.2. Summary of Animal Data Relevant to AEGL-1

Data are not available on responses in animals that would be consistent with AEGL-1 effects.

5.3. Derivation of AEGL-1

Exposure-response data were not available for developing AEGL-1 values for phosphorus oxychloride (Table 5-4).

TABLE 5-4 AEGL-1 Values for Phosphorus Oxychloride

10 min	30 min	1 h	4 h	8h
Not recommended				

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative exposure-response data in humans are not available for development of AEGL-2 values for phosphorus oxychloride. Information regarding the human experience is based on qualitative and semi-quantitative information regarding signs and symptoms (respiratory tract irritation that might persist for extended periods and ocular and dermal irritation) of exposed individuals. The information in these reports suggest very brief exposure to phosphorus oxychloride at low concentrations (1.6-3.2 ppm) might cause irritation severe enough to impair egress from a contaminated area. Additionally, data from animal studies suggest that acute exposure to phosphorus oxychloride might cause contact irritation damage (e.g., corneal opacities) that could be irreversible. However, definitive exposure concentration and duration measurements were lacking for these animal studies, thereby preventing exposure-response assessments for AEGL-2 development.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data on effect severity consistent with AEGL-2 were based on qualitative descriptions of responses in animals exposed to lethal or near-lethal concentrations. Signs of exposure in these studies were consistent with extreme irritation of the eyes, nasopharyngeal region, and the respiratory tract. However, exposure concentration data and exposure duration data were not available.

6.3. Derivation of AEGL-2

Exposure-response data were not available for developing AEGL-2 values for phosphorus oxychloride (Table 5-5). The lack of information regarding the exposure-response relationship makes estimating AEGL-2 values by reducing AEGL-3 values difficult to justify.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Information is not available regarding lethality in humans exposed to phosphorus oxychloride.

TABLE 5-5 AEGL-2 Values for Phosphorus Oxychloride

10 min	30 min	1 h	4 h	8h
Not recommended				

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data are based on 4-h LC_{50} values for rats and guinea pigs. Two 4-h LC_{50} values are available for rats: 48.4 ppm (Weeks et al. 1964) and 32 ppm (Marhold 1972 as cited in RTECS 2009, unverifiable). A single 4-h LC_{50} for guinea pigs is 52.5 ppm (Weeks et al. 1964). The range of exposure used to determine these median lethal concentrations, however, were not reported. Therefore, it is not possible to assess the exposure-response relationship. The available data suggest that species variability in the lethal response to phosphorus oxychloride is not great. However, there is still uncertainty regarding the range of susceptibility among species because data are available from only one well described study on two species.

7.3. Derivation of AEGL-3

In lieu of additional data, the available 4-h LC_{50} values may be considered for developing AEGL-3 values for phosphorus oxychloride. Because the rat appears to be a slightly more sensitive species than the guinea pig, the 4-h LC_{50} of 48.4 ppm identified by Weeks et al. (1964) was used as the basis for the AEGL-3 values. The 32-ppm value reported in RTECS (2009) was not verified and, therefore, was not used.

In the absence of complete data regarding the exposure-response curve and assuming that the difference between nonlethal and lethal exposures is small, the lethality threshold was estimated to be one-third of the 4-h rat LC_{50} (48.4 ppm/3 = 16.1 ppm). This extrapolation is also justified because many respiratory tract irritants have exposure-response relationships in which the transition from progressive irritation and repairable epithelial tissue damage to lethal pulmonary damage occurs abruptly. A total uncertainty factor of 30 (10 for interspecies variability and 3 for intraspecies variability) was used. The interspecies uncertainty factor of 10 was maintained because there are data on only two species (a single 4-h LC_{50} each for rats and guinea pigs) and no lethality data in humans. Additionally, the study by Weeks et al. (1964) showed rats to be notably more sensitive to phosphorus oxychloride (4-h LC_{50} of 48.4 ppm) than to phosphorus trichloride (4-h LC_{50} of 104. 3 ppm). Although signs of exposure in humans are qualitatively similar to those observed in laboratory animals, there are no quantitative exposure-response data in humans. An intraspecies uncertainty factor of 3 was selected because a critical mechanism of phosphorus oxychloride toxicity appears to involve irritation and destruction of pulmonary mucosal surfaces; lethality resulting, at least in part, from damage to respiratory tract epithelium. It is assumed that a basic contact irritation mechanism would not vary greatly among individuals and that a 3-fold reduction would be sufficient to protect individuals with moderately compromised respiratory function. Further reduction of the AEGL-3 values by a greater uncertainty factor would result in values inconsistent with occupational exposures reported by Sassi

(1954), where repeated exposures to concentrations up to 3.2 ppm resulted in irritation and minor respiratory difficulties but not death. There are no data available to determine a time-scaling factor. The concentration-exposure-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. Because of uncertainties in extrapolating a 4-h exposure to a 10-min exposure, the 10-min AEGL-3 is set equivalent to the 30-min AEGL-3 rather than using exponential scaling. The derivation of AEGL-3 values is shown in Appendix A and the resulting values are summarized in Table 5-6.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

The available toxicity data for phosphorus oxychloride indicate that irritation of the skin, eyes, nose, and respiratory tract are the most notable and often reported signs of toxicity. Although these end points relevant to AEGL-1 and AEGL-2 values, quantitative exposure-response data are lacking for development of these values. Quantitative data on lethality in animals were available and were considered appropriate for the basis of AEGL-3 development. The data were, however, limited to a single study and two species.

8.2. Comparison with Other Standards and Guidelines

The World Health Organization (WHO 1989) reported that exposure guidelines for phosphorus oxychloride range from 0.05-3 mg/m^3 (0.008-0.48 ppm) in different countries. Standards and criteria for phosphorus oxychloride are presented in Table 5-7.

8.3. Data Quality and Research Needs

Although qualitative data are available regarding the acute inhalation toxicity of phosphorus oxychloride in humans, quantitative exposure-response data are lacking. Animal data include one study reporting LC_{50} values in rats and guinea pigs. The animal data were sufficient for developing AEGL-3 values. However, there are no data pertaining to the nonlethal responses in animals following inhalation exposure to phosphorus oxychloride. There are also insufficient data for determining the range of susceptibility among different species or between the test animal species and humans.

TABLE 5-6 AEGL-3 Values for Phosphorus Oxychloride

10 min	30 min	1 h	4 h	8h
1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

TABLE 5-7 Standards and Guidelines for Phosphorus Oxychloride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended				
AEGL-2	Not recommended				
AEGL-3	1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm
TLV-TWA (ACGIH)[a]					0.1 ppm
REL-TWA (NIOSH)[b]					0.1 ppm
REL-STEL (NIOSH)[c]	0. 5 ppm (15 min)				
MAK Spitzenbegrenzung (Germany)[d]					1.33 mg/m^3 (0.2 ppm)
MAC (The Netherlands)[e]					0.6 mg/m^3 (0.1 ppm)

[a]TLV-TWA (Threshold Limit Value-time-weighted average of the American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[b]REL-TWA (recommended exposure limits-time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH-TLV-TWA.
[c]REL-STEL (recommended exposure limits-short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH-TLV-STEL.
[d]MAK Spitzenbegrenzung (Kategorie II,2) [maximum workplace concentration (peak limit category II,2)] (DFG 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min, with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK.
[e]MAC (maximaal aanvaarde concentratie [maximum accepted concentration]), Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is analogous to the ACGIH-TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PHOSPHORUS OXYCHLORIDE

Derivation of AEGL-1

AEGL-1 values are not recommended because insufficient data. Absence of AEGL-1 values does not imply that exposure below the AEGL-3 values are without adverse effects.

Derivation of AEGL-2

AEGL-2 values are not recommended because of insufficient data. Absence of AEGL-2 values does not imply that exposure below the AEGL-3 values are without serious or possibly irreversible adverse effects.

Derivation of AEGL-3

Key study:	Weeks et al. 1964
Toxicity end point:	Lethality threshold of 16.1 ppm in rats, estimated by 3-fold reduction in 4-h LC_{50} of 48.4 ppm.
Scaling:	$C^n \times t = k$ (n = 3 for extrapolating from longer to shorter exposure periods and n = 1 for extrapolating from shorter to longer exposure periods) $(16.1 \text{ ppm})^1 \times 4 \text{ h} = 64.4 \text{ ppm-h}$ $(16.1 \text{ ppm})^3 \times 4 \text{ h} = 16{,}693.12 \text{ ppm-h}$
Uncertainty factors:	10 for interspecies variability 3 for intraspecies variability
10-min AEGL-3	1.1 ppm, set equal to the 30-min AEGL-3
30-min AEGL-3	$C^3 \times 0.5 \text{ h} = 16{,}693.12 \text{ ppm-h}$ $C = 32.2 \text{ ppm}$ 30-min AEGL-3 = 32.2 ppm/30 = 1.1 ppm
1-h AEGL-3	$C^3 \times 1 \text{ h} = 16{,}693.12 \text{ ppm-h}$ $C = 25.56 \text{ ppm}$ 1-h AEGL-3 = 25.56 ppm/30 = 0.85 ppm

4-h AEGL-3	$C^3 \times 4$ h = 16,693.12 ppm-h C = 16.1 ppm 4-h AEGL-3 = 16.1 ppm/30 = 0.54 ppm
8-h AEGL-3	$C^1 \times 8$ h = 64.4 ppm-h C = 8.05 ppm 8-h AEGL-3 = 8.05 ppm/30 = 0.27 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR PHOSPHORUS OXYCHLORIDE

Derivation Summary for Phosphorus Oxychloride

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Toxicity End Point: Not applicable				
Time Scaling: Not applicable				
Concentration/Time Selection/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustments: Not applicable				
Data Adequacy: Neither quantitative exposure-response data nor odor threshold data were available for assessing AEGL-1 type effects for phosphorus oxychloride. Therefore, AEGL-1 values are not recommended. The absence of AEGL-1 values does not imply that exposure below AEGL-3 levels is without effect.				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Toxicity End Point: Not applicable				
Time Scaling: Not applicable				
Concentration/Time Selection/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustments: Not applicable				

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

Data adequacy: Exposure-response data on nonlethal toxic responses were not available for developing AEGL-2 values for phosphorus oxychloride. The absence of such data precludes estimating AEGL-2 values by reducing AEGL-3 values. Therefore, AEGL-2 values are not recommended. The absence of AEGL-2 values does not imply that exposure below AEGL-3 levels is without serious or possibly irreversible effect.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

Reference: Weeks, M.H., N.P. Mussleman, P.P. Yevich, K.H. Jacobson, and F.W. Oberst. 1964. Acute vapor toxicity of phosphorus oxychloride, phosphorus trichloride and methyl phosphonic dichloride. Am. Ind. Hyg. Assoc. J. 25:470-475.

Test Species/Strain/Number: Rats (strain not specified)/20 per group

Exposure Route/Concentrations/Durations: Inhalation/concentrations varied but not specified/4 h

Toxicity End Point: 4-h LC_{50} (48.4 ppm) for guinea pigs

Time Scaling: $C^n \times t = k$, n = 3 for extrapolating from longer to shorter exposure periods and n = 1 for extrapolating from shorter to longer exposure periods

Concentration/Time Selection/Rationale: A 3-fold reduction of 4-h LC_{50} (48.4 ppm/ 3 = 16.1 ppm) for rats (the more sensitive species) was considered an estimate of the lethality threshold

Uncertainty Factors/Rationale:
Total Uncertainty: 30
Interspecies: 10
Intraspecies: 3 was considered sufficient because the primary mechanism of action involves a direct effect on respiratory epithelium which is unlikely to vary greatly among individuals. The factor also is considered to be adequate for the protection of individuals with moderately compromised respiratory function. Additional reduction of the AEGL-3 values by a greater uncertainty factor would result in AEGL-3 values that are inconsistent with occupational data and other guidelines.

Modifying Factor: None applied

Animal-to-Human Dosimetric Adjustments: Insufficient data

Data Adequacy: LC_{50} values available for only two species. These data were considered sufficient for developing AEGL-3 values. Interspecies variability remains uncertain because of the lack of data in additional species and definitive exposure data in humans.

APPENDIX C

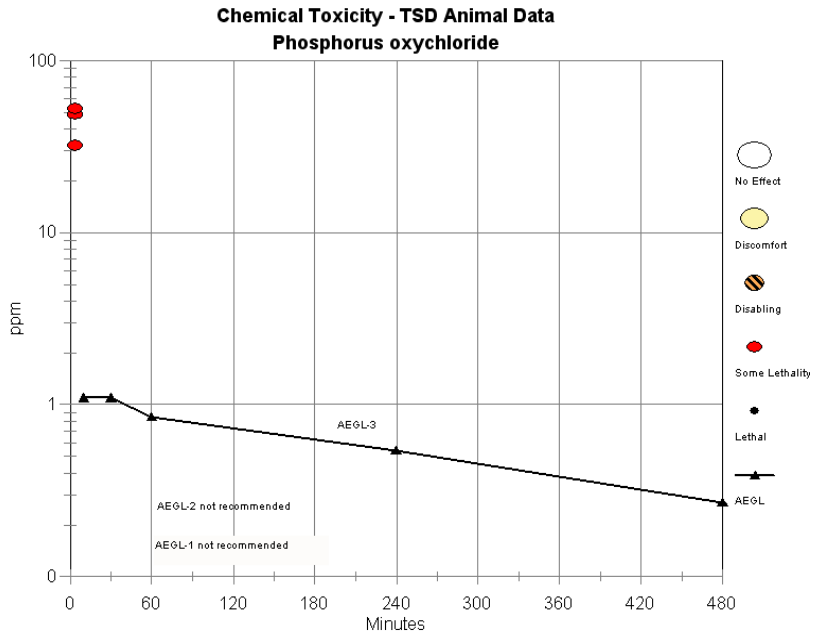

FIGURE 5-1 Category plot for phosphorus oxychloride.